PROFILE OF GENERALISED CONVULSIVE STATUS EPILEPTICUS IN CHILDREN

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CERTIFICATE

This is to certify that the dissertation entitled **"Profile of Generalised Convulsive Status Epilepticus in Children"** submitted by **Dr.S.Ramesh** to the Faculty of Pediatrics, The Tamil Nadu Dr.M.G.R. Medical University, Chennai in partial fulfillment of the requirement for the award of M.D. Degree Branch VII (Pediatrics) is a bonafied research work carried out by him under our direct supervision and guidance.

Dean,
Govt. Rajaji Hospital,
Madurai Medical College,
Madurai.

Prof. & HOD,
Institute of Child Health &
Research Centre,
Govt. Rajaji Hospital,
Madurai Medical College,
Madurai.

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CONTENTS

Introduction

INTRODUCTION

Status Epilepticus (SE) is defined as a continuous convulsion lasting longer than 30min or the occurrence of serial convulsions between which there is no return of consciousness [1]. SE is a condition which most likely will not terminate rapidly and spontaneously; and requires prompt intervention [2]. For all practical purpose, any child who continue to convulse when brought to the emergency room should be treated as a case of status epilepticus [2,3].

SE is the most common emergency in Pediatric Neurology. It may be classified as Generalized or Partial. Generalised Tonic Clonic Seizure (GTCS) is the predominate type in SE [1].

Etiology:

There are three major subtypes of SE in children.

1) Prolonged febrile seizures; 2) Idiopathic SE, in which a seizure develops in the absence of an underlying Central Nervous System (CNS) lesion or insult; and 3) Symptomatic SE, when seizure occurs as a result of an underlying neurologic disorder or a metabolic abnormality [1].

A febrile seizure lasting for more than 30 min, particularly in a child younger than 3 years of age, is the most common cause of SE. The Idiopathic group includes epileptic patients who have had sudden withdrawal of anticonvulsants (especially Benzodiazepines and Barbiturates) followed by SE. Epileptic children who are given anticonvulsants on an irregular basis or who are non compliant with drug treatment, are more likely to develop SE. SE may be the initial presentation of epilepsy. Sleep deprivation and intercurrent infections render the epileptic patients more susceptible to SE. The mortality and morbidity among patients with prolonged febrile seizures and idiopathic SE are low [1].

SE owing to other causes has a much higher mortality rate and the cause of death usually is directly attributable to the underlying etiology. Some of the causes for Symptomatic SE are Hypoxic Ischemic Encephalopathy (HIE) sequelae, encephalitis, meningitis, congenital brain malformation, inborn errors of metabolism, electrolyte imbalance and brain tumours, particularly in the frontal lobe [1].

Management:

Early and effective treatment is essential to prevent prolonged seizures. Studies of prolonged seizures have established that the longer the duration of seizure before treatment ,the more difficult to stop it and greater the risk for long term neurological sequelae [3].

Domicilary Treatment:

Prolonged seizures or clusters of seizures in children with known epilepsy can sometimes be managed at home with rectal Diazepam to prevent or abort SE [4]. This is effective and can decrease the cost spent on the evaluation and further treatment of these patients [3]. A rectal Diazepam gel is commercially available, or the intravenous preparation can be given rectally (0.4mg/kg) through a lubricated syringe [4]. Only a single prehospital dose of rectal Diazepam should be given by the caretakers [3]. If the rectal dose fails to stop the seizures, the child should be bought to the emergency service immediately [4].

Hospital Treatment:

When a convulsing child presents to the emergency room, initial assessment should be rapid with directed history and physical examination. Confirm the diagnosis by observing the ictal behaviour and document the seizure duration. Note the nature of onset of seizure activity, history of fever or intercurrent illness, past history of seizures, medications and compliance, head injury, drug ingestion and toxin exposure. Perform brief general and neurological examination, assess oxygenation and ventilation, note cyanosis, peripheral perfusion, pupil size, asymmetry on neurological examination, petechiae or purpura, vesicles and deformity or soft tissue injury of head [2]. A comprehensive examination should be undertaken once the seizures are controlled [1].

Initial treatment of patients begins with an assessment of the respiratory and cardiovascular systems.

1. The oral airway is secured and inspected for patency. The pulse, temperature, respiration and blood pressure are recorded.

2. Excessive oral secretions are removed by gentle suction and a properly fitting face mask attached to oxygen is applied.
3. If patients do not respond to oxygen by mask, ventilation with bag and mask can be started. Consideration should be given to intubation and assisted ventilation [1] during any stage in seizure management.
4. A nasogastric tube is placed in position [1] to reduce the chances for regurgitation and aspiration.
5. Venous access is established next. Blood is withdrawn for measurement of glucose, electrolytes and anticonvulsant level, if indicated. Other tests (i.e. a toxic screen) are performed as indicated [4].
6. After blood is withdrawn, an intravenous infusion of saline solution is started [4]. Shock, if present, is corrected with Normal saline boluses.
7. Infuse Dextrose (2ml/kg of 25% solution) if hypoglycemia is confirmed or if Dextrostix is not available for immediate confirmation. Hyperglycemia has no adverse affect on outcome of SE [2].
8. Hyperthermia occurs frequently in SE and is primarily due to motor activity. Given the damaging effects of fever in patients with central nervous injury, hyperthermia should be treated promptly by passive cooling [3].

Anticonvulsant Treatment:

In the convulsing patient, initial supportive, therapeutic and diagnostic measures need to be conducted simultaneously. The goal of anticonvulsant treatment is the rapid termination of clinical and electrical seizure activity by the prompt administration of appropriate drug in adequate doses with attention to the possibility of complicating apnea, hypoventilation and other metabolic abnormalities [3].

1. Drugs should always be administered intravenously (I.V.) in the management of SE; the intramuscular (I.M.) route is unreliable because some drugs are sequestrated by muscles [1]. If

I.V. access is not immediately available, intra-osseous access (I.O.) can be used safely in children [2].

2. It is essential to have resuscitation equipment at the bedside and the ability to intubate and ventilate the patient immediately if respiratory depression occurs [1].
3. Many anticonvulsant protocols and treatment guidelines are reported from various institutions and groups. Most importantly, every institution should have a well established treatment protocol depending upon the local availability of drugs [3]. The timing, route and adequacy of dosages of drugs used are important. Sufficient time must be allowed for the drugs to act before more of the same medication or another medication is used [2].

The management protocol commonly used is as follows:

(PROCEED TO THE NEXT STEP, IF SEIZURE IS NOT CONTROLLED)

O minutes: A Benzodiazepine (Diazepam, Lorazepam or Midazolam) may be used intially, because these are effective for immediate control of prolonged tonic clonic seizures in most children.

Diazepam is given I.V. in a dose of 0.1-0.3mg/kg at a rate no greater than 2mg/min. Respiratory depression and hypotension can occur, especially if administered with a Barbiturate. The drug is effective but has a short half life and seizures may recur unless a longer acting anticonvulsant is administered simultaneously [1].

Lorazepam is an equally effective short term anticonvulsant, with a longer duration of action and decreased likelihood of producing hypotension and respiratory arrest. The recommended dose is 0.05-0.1mg/kg I.V [1] ; a maximum of 4mg/dose is administered at rate of2mg/min [2].

Midazolam is given at a dose of 0.15-0.3mg/kg I.V. or I.M., if there is no I.V / IO access [2].

10 minutes: Repeat Inj. Diazepam or Lorazepam in the same dose (2nd dose) [2]

20 minutes: If seizure persist or even if the convulsive activity ceases after Diazepam or Lorazepam therapy, Phenytoin is given immediately [1].

Phenytoin is administered at a loading dose of 20mg/kg I.V. slowly over 20min (1mg/kg/min). The drug should be diluted only with normal saline [2].

Fosphenytoin is a prodrug of Phenytoin, that can be used instead of Phenytoin by I.V. or I.M. route. The loading dose of 30mg/kg is to be administered I.V. over 10min (3mg/kg/min) [2]

40 minutes: Inj. Phenytoin 10mg/kg over 10min (2nd dose)

or

Inj. Fosphenytoin 5mg/kg over 5min (2nd dose) is given [2].

Electrocardiography (ECG) is recommended during the loading phase to identify arrhythmias and bradycardia, a rare complication in children.

Systemic hypotension may also complicate I.V. Phenytoin therapy

If the seizures do not recur, a maintanence dose of 3-9 mg/kg divided into two equal doses daily is begun 12-24 hrs later. Serum Phenytoin levels should be monitored because the maintenance dose varies considerably with age [1].

60 minutes: **Phenobarbitone** is given in a loading dose of 15-20 mg/kg at the rate of 2mg/kg/min over 10 minutes in 1-2 ml/kg of NS or 5% Dextrose solution.

Phenobarbitone is a depressant drug and can lead to sedation and respiratory depression, especially when administered after a Benzodiazepine. Thus during or following a loading dose, assisted ventilation is usually required [2] .

With control of seizures, Phenobarbitone is given in a maintianence dose of 3-5 mg/kg/24hrs divided into two equal doses [1].

If SE persists beyond this stage (i.e. longer than 60 min.) it is called **Refractory Status Epilepticus (RSE)** and it becomes more life threatening.

Constant I.V. infusion of either

Midazolam (0.2mg/kg bolus, 20-400 micro gm/kg/hr infusion)

or

Propofol (1-2mg/kg, 2-10mg/kg/hr infusion) has been effective in managing seizures, during SE, unresponsive to other anticonvulsants [1].

If seizures continue, serious consideration is given to induction of **Barbiturate Coma.** In an intensive care unit, the patient is placed on a ventilator and a continuous Electroencephalographic (EEG) monitor. The initial I.V. loading dose of Thiopental is 2 to 4mg/kg and is then titrated to achieve a burst suppression EEG pattern. Barbiturate coma is continued for atleast 48hrs, followed by cessation of thiopental until the serum Phenobarbital level falls to therapeutic range. Barbiturate coma requires careful monitoring because hypotension due to myocardial depression often requires presser therapy [1].

The other drugs that can be used for RSE are Diazepam infusion, Paraldehyde, Pentobarbital coma and ultimately General anesthesia with Halothane or Isoflurane and neuromuscular blockade [1,2].

If the seizures are controlled at any of the above step, the child should be placed in recovery position, wherever applicable; the vital signs are closely monitored and the child is observed carefully for seizure recurrence [2]. Postictal confusion usually resolves over several hours and the failure to gradually improve must prompt a search for other causes such as hypoglycemia, CNS infection, CNS

vascular event, toxic encephalopathy, and Non convulsive Status Epilepticus (NCSE). In particular NCSE can present with subtle behavioural changes, which can be easily discounted unless the clinician maintains a high index of suspicion. NCSE can be diagnosed by continuous EEG monitoring [3].

Further Management :

After the control of seizures and stabilization, identify precipitating factors, modify drug treatment and start maintainence therapy. Blood is obtained for complete blood count, urea, creatinine and lactate levels. Blood and urine may be obtained for metabolic studies and toxicological screening [1]. Arterial blood gas analysis is not routinely indicated[2]. It is wise to monitor oxygen saturation with an Oximeter. Examination of CSF is imperative, if meningitis or encephalitis is considered, unless there is contraindication to the procedure [1]. In this case, appropriate antibiotics should be administered, followed by imaging studies, before a lumbar puncture is attempted. CT scan is also required in focal seizures or focal deficit, with history of trauma or bleeding disorder [2].

Follow Up:

A long term antiepileptic should be maintained In children with progressive neurological disorder or with a history of recurrent seizures before the onset of SE. However in children with initial attack of Idiopathic SE, anticonvulsant is maintained arbitrarily for 3 months and then discontinued if the child remains asymptomatic [1].

Prognosis:

The mortality rate of SE is approximately 5%. The greatest number of deaths occur in the symptomatic group, most of whom have a serious and life threatening CNS disorder. In the absence of a progressive neurologic insult or metabolic disorder, the morbidity from SE is low [1]. Thus the prognosis of SE is related to the etiology and duration of seizures [2].

Review Of Literature

REVIEW OF LITERATURE

Seizures may have various appearances and of different causes. Some are recurrent and represent the various types of epilepsy, whereas others are single events Status Epilepticus (SE) represents a special epilepsy syndrome and it is a true neurologic emergency [5] that requires immediate and vigorous management; and at times poses a therapeutic challenge to the treating physician. If not managed promptly, it may result in significant neuromorbidity and mortality [6].

SE is recognized as a distinct entity since 1824 [5]. However major advances appeared since the 1980 Santa Monica International Conference on the treatment of SE, which included recognition of Subtle SE, Nonconvulsive status, new agents for SE and treatment of Drug Resistant SE [5].

Definition:

In the 'Dictionary of Epilepsy' , Gastaut (1973) defined SE as a "condition characterized by an epileptic seizure that is sufficiently prolonged or repeated at sufficiently brief intervals so as to produce an unvarying and enduring epileptic condition" [7]. The main advantage of this definition is that it encompasses a variety of different seizure types [8].

In 1981, the International League Against Epilepsy (ILAE) defined SE as a seizure that "persists for a sufficient length of time or is repeated frequently enough that recovery between attacks does not occur". The lack of specific duration of the seizures has made this definition difficult to use [9].

More recent publications have defined SE as seizures that persist for 20 to 30 min, which is an estimate of the duration necessary to cause injury to CNS neurons [9]. Thus SE is defined as single seizure or multiple episodes of seizures lasting more than 30 min without regaining consciousness in between [3]. This precise definition of SE although useful for epidemiological analysis and evaluation of therapeutic interventions, does not address the urgency experienced by clinicians when confronted with a convulsing child, irrespective of how long the episode has lasted. It therefore seems more appropriate to take a pragmatic view and consider SE as the severe and of a continuum encountered

during the progressive evolution of an unrelenting seizure, which may culminate with potentially life threatening complications [3].

The current trend in the treatment of SE eliminates a specific duration for the diagnosis of SE and emphasises diagnostic criteria aimed at improving treatment outcome. This trend towards a shorter seizure duration is supported by experimental evidence [9].

The operational definition of SE is “either continuous seizures lasting at least five minutes or two or more discrete seizures between which there is incomplete recovery of consciousness”. This definition differs from that of serial seizures, which are two or more seizures occurring over a relatively brief period (i.e. minutes to many hours), but with the patient regaining consciousness between the seizures [9]. However the serial seizures requires the same vigorous management as SE [7].

Clinical Features:

When first seen, patients with SE are unresponsive and usually have clinically obvious seizures: such as tonic, clonic or tonic-clonic movements of the extremities. With time, however the clinical manifestations often become subtle, and the diagnosis requires careful observation. Patients may have only small amplitude twitching movements of the face, hands or feet, or nystagmoid jerking of the eyes. Some patients have no observable, repetitive motor activity, and the detection of ongoing seizures require Electroencephalography (EEG). Electrographic SE of this type may be more common in hospitalised, comatose patients than previously thought. Patients who have electrographic SE with little or no motor activity (including patients paralysed for airway management) are still at risk for CNS injury and require prompt treatment. Myoclonic SE, which is usually seen in patients after prolonged anoxia or other severe metabolic insults, consists of very brief, sudden movements of restricted parts of the body that may be triggered by external stimuli, such as mechanical ventilation [9].

Classification:

Most of the classification schemes divide SE into Convulsive and Non convulsive types. SE is then further defined utilizing the ILAE classification [8].

I. Convulsive SE:

A. Generalised Convulsive SE

1. Tonic clonic SE
2. Tonic SE
3. Myoclonic SE
4. SE complicating Infantile spasms

B. Focal Convulsive SE

1. Partial elementary SE
2. Partial SE with secondary generalisation

II. Non-convulsive SE

A. Generalised Non convulsive SE

1. Atonic, Akinetic, Myoclonic (Minor Motor) SE
2. Absence SE

B. Focal non convulsive SE

Partial complex SE

For individual episodes of SE, an adequate description should include etiology, physiologic expression of seizures activity and anatomic locus of seizure discharge [8]. .Generalised Convulsive SE (GCSE) is the most common and most dangerous type. GCSE can be further divided into overt and subtle types. Overt GCSE is defined as recurrent convulsions without complete recovery between seizures. Subtle GCSE is defines as the stage of GCSE when the patient is in continuous coma but only subtle motor convulsions are seen [10].

Patients were classified as having one of these two types of SE according to the following operational definitions. Overt GCSE was considered present when there were two or more generalized convulsions, without full recovery of consciousness between seizures, or continuous convulsive activity for more than 5 min [9,10]. Subtle GCSE was considered present when the patient had coma and ictal discharges on the EEG, with or without subtle convulsive movements (rhythmic twitching of the arms, legs, trunk or facial muscles; tonic eye deviation; or nystagmoid eye jerking). If the investigator required an EEG to diagnose GCSE, the patient was considered to have subtle GCSE

[10] (Electroencephalographic SE) [9].

Although usually not considered in discussions of SE, some epileptic conditions that are unique to childhood have sufficient duration or recurrence rate to satisfy the formal definition; however, these epileptic syndromes are not usually approached diagnostically or therapeutically as SE [7].

Childhood conditions meeting the definitions of SE [7]

1. West syndrome (Infantile spasms with hypsarrythmia)
2. Lennox Gastaut syndrome
3. Landau Kleffner syndrome
4. Pykno epilepsy
5. Epilepsia partialis continua (Rassmussen's encephalitis)
6. Continuous spike and wave during sleep.
7. Continuous occipital spike and wave during sleep.

SE can also be classified based on the age of occurrence [11]

1. SE confined to early childhood

- Neonatal SE
- SE in specific neonatal epilepsy syndromes
- Infantile spasms

2. SE confined to later childhood

- Febrile SE
- Status in childhood partial epilepsy syndromes
- SE in myoclonic astatic epilepsy
- Electrical SE during slow wave sleep
- Landau Kleffner syndrome

3. SE occurring in childhood and adult life

- Tonic Clonic SE
- Absence SE
- Epilepsia partialis continua
- SE in coma
- Specific forms of SE in mental retardation
- Syndromes of myoclonic SE
- Simple partial SE
- Complex partial SE

4. SE confined to adult life

- de novo absence status and late onset

In 1980, Santa Monica International Symposium classified SE as follows [5]:

1. Primary GCSE

- Tonic clonic status
- Myoclonic status
- Clonic-tonic-clonic status

2. Secondary GCSE

- Tonic clonic status with partial onset
- Tonic status
- Subtle GCSE

3. Simple partial status

- Partial motor status
- Unilateral status
- Epilepsia partialis continua
- Partial sensory status
- Partial status with vegetative, autonomic or affective symptoms

4. Non convulsive status:

- Absence status – typical or atypical
- Complex partial status

Most SE episodes in children appear to be generalised convulsive in character. Of those SE episodes beginning with partial seizures, most secondarily generalise. Careful history taking and observation suggests that the majority (64% of adults and children) of all SE episode begin as partial seizures that generalize so that the final character is generalized [12].

Etiology:

Status epilepticus may be the presentation of wide spectrum of disease processes [13]:

1. Infective conditions: Tuberculous Meningitis
   Pyogenic Meningitis
   Viral Encephalitis
2. Vascular conditions : Cortical vein thrombosis,
   Cerebral artery thrombosis
   Vasculitis
3. Neurocutaneous syndromes : Neurofibromatosis

		Tuberous Sclerosis
		Sturge Weber syndrome
		Incontinentia Pigmenti
4. Congenital malformations	:	Absence of Corpus Callosum
		Hydrocephalus
		Porencephaly
		Lissencephaly
		Schizencephaly
5. Matabolic conditions	:	Hypoglycemia
		Hypocalcemia
		Hypomagnesemia
		Hyponatremia
		Hypernatremia
		Uremic encephalopathy
		Reye's syndrome
6. Congenital metabolic errors	:	Phenyl Ketonuria
		Urea cycle disorders
		Lactic acidosis
		Menke's kinky hair disease
7. Degenerative conditions	:	Generalised Gangliosidosis
		Alper's disease
		Batten's disease
8. Tumours	:	Intracranial space occupying lesions
9. Head trauma	:	Contusions and lacerations of brain
		Subdural haematoma [13]
10. Toxic encephalopathy	:	Lead [6,7]

Certain etiologies are unique to the pediatric population, including those responsible for

recurrent neonatal seizures such as traumatic subarachnoid hemorrhage, neonatal HIE and inborn errors of metabolism. Fever as the sole precipitating event of recurrent seizures and SE is also seen only in the young patients [7].

For simplification, the variable etiologies of GCSE can be classified as follows [8]:

1. Acute encephalopathies

Most common - Meningitis

Encephalitis

Dehydration

Electrolyte disorders

Others - Head trauma

Hypoxic or Anoxic injury

Toxin ingestion

Hypoglycemia

Hypocalcemia

2. Chronic Encephalopathies:

Remote symptomatic brain injury

Cerebral palsy

Brain malformations

Neurocutaneous syndromes

Progressive CNS degenerative disease

3. Idiopathic (Cryptogenic) seizures:

Febrile

Afebrile

Seizures in the acute category are often difficult to control and are associated with a higher mortality [9]. In contrast to adults, brain tumours and alcohol are seldom implicated in the etiology of acute SE in children [8.] It has been observed that the classical symptoms and signs of acute bacterial meningitis may be absent in SE and a high index of suspicion for infection in the child with SE and

fever is paramount. Systemic disorders like hypertension may occasionally present with SE [6].

In general, patients with SE due to chronic processes respond well to anticonvulsant treatment and they recover from the acute episode of seizure [9]. With chronic encephalopathies, the lesions are widespread and do not have the frontal predominance reported in series of adults with SE [8].

The most important cause for SE varies with the age of the child. Whereas febrile SE is the most common cause in children less than 5 years of age, trauma and infections are important in older children. Severe hypoxic encephalopathy and in born error of metabolism may present with SE in the newborn [6].

The important risk factors for SE are a history of epilepsy, younger age of patient, genetic predisposition and acquired brain insult [6]. Precipitating factors leading to SE can often be identified in children with chronic encephalopathies [8]. The important precipitating factors include fever, irregular intake or sudden discontinuation of antiepileptic drugs, overdose of antiepileptic medications, sleep deprivation, fatigue, metabolic derangements, concomitant use of other medications (Theophylline, Amphetamine, Isoniazid, Phenothiazines), psychotic disturbances, hyperventilation and intermittent photic stimulation [6].

Pathophysiology:

The fundamental pathophysiology of SE involves a failure of the mechanisms that normally abort an isolated seizure. This failure can arise from abnormally persistent, excessive excitation or ineffective recruitment of inhibition. The relative contributions of these factors are poorly understood. The temporal and spatial determinations of SE are also relatively unknown; experimental studies suggest that there is induction of reverberating seizure activity between, for example, hippocampal and parahippocampal structures and that the seizures progress through a sequence of distinct electrographic changes [9].

It is likely that numerous mechanisms are involved, depending on the underlying cause:

1. Excessive activation of excitatory amino acid receptors by Glutamate and Aspartate (excitatory amino acid neurotransmitters) may cause SE [9,13].
2. Decreased Gama Amino Butyric Acid (GABA) level may also precipitate convulsions [13]. SE can

be caused by Penicillin and related compounds that antagonise the effects of GABA. The failure of inhibition may be due in some cases to a shift in the functional properties of the GABA receptor that occurs as seizures become prolonged [9].

3. Repeated subconvulsive stimulation i.e. kindling may induce SE [13].
4. Abnormal pathological changes in brain like glioma, hamartomas, arterio venous malformations, gliosis particularly in Amygdala precipitate SE [13].
5. Substantia nigra may be responsible for initiating convulsions [13].

Pathogenesis:

SE lasting approximately 30 to 45 min can cause cerebral injury, especially in limbic structures such as the hippocampus and seizure activity itself is sufficient to damage the CNS. This damage is partly a consequence of Glutamate mediated excitotoxicity and does not appear to be due primarily to an excessive metabolic demand imposed by repetitive neuronal firing. The superimposition of systemic stresses such as hyperthermia, hypoxia or hypotension exacerbates the degree of neuronal injury in animal models of SE, a finding consistent with the empirical observations in humans [9].

In many encephalopathies, including the SE poor cerebral blood perfusion is the final common pathway. The decrease in local cerebral blood flow below a critical threshold, results in the following: energy failure, tissue acidosis, disturbed ion homeostasis (characterized by enhanced cellular Potassium efflux and Sodium and Calcium influx), membrane depolarization and cytotoxic edema. A massive release of the excitatory amino acid neurotransmitters, Glutamate and Aspartate, and the activation of Glutamate receptors [including N- methyl d-Aspartate (NMDA) receptors) have been ascribed a major pathophysiological significance. This triggers further membrane depolarization and additional accumulation of free cytosolic Calcium ions by cellular influx, release from intracellular compartments and disturbed extrusion mechanisms. The Calcium ion accumulation then seems to play a key role in propagation of the process eventually culminating in irreversible neuronal damage, in that it leads to an activation of series of neurotoxic events, such as lipid peroxidation, free radical generation, activation of proteolytic enzymes and pathological gene activation. In addition, microglial

cells seem to have a significant role, in that they are important source of free radicals [14].

Pathology:

At autopsy, the cerebral hemispheres are congested and edematous with petechial & microscopic hemorrhages. The most vulnerable areas in brain are Hippocampus, Amygdala, Cerebellum, Middle cortical layer and Thalamus [13.] At the cellular level, ischemic cellular changes due to an increase in metabolic demand, depletion of glucose stores and oxygen supply are the earliest histologic findings [6]. This is followed by neuronophagia, microglial and astrocyte proliferation and neuronal loss [13]

Phases of Status Epilepticus:

The physiological changes in SE are often divided into two phases (Phase 1 and Phase 2) if the convulsion occurs for about 30-60 min. These changes do not necessarily occur in all cases. The rate and extent of physiological changes are dependant on many other factors like.

1. Anatomical site of epileptic focus
2. Severity of the seizure
3. Underlying etiology and
4. the treatment employed

The phases of changes is useful in devising a rational plan for therapy [11,13].

Phase I:

During this phase, cerebral metabolism is greatly increased because of seizure activity, but physiological mechanisms are sufficient to meet the metabolic demands, and cerebral tissue is protected from hypoxia or metabolic damage. The major physiological changes are related to the greatly increased cerebral blood flow and metabolism, massive autonomic activity and cardiovascular changes [11].

Phase 2:

During this phase, the greatly increased cerebral metabolic demands cannot be fully met, resulting in hypoxia and altered cerebral and systemic metabolic patterns. Autonomic changes

persists and cardiorespiratory functions may progressively fail to maintain homeostasis. The tansition from phase 1 to 2 occurs after about 30-60 min of continuous seizures [11].

The physiological changes in the two phases of SE can be tabulated as follows:

Features	Phase 1 (Compensation)	Phase 2 (Decompensation)
Cerebral changes	Increased blood flow Increased metabolism Energy requirements matched by supply of oxygen & glucose (increased glucose and oxygen utilization) Increased lactate concentration Increased glucose concentration	Failure of cerebral auto regulation; thus cerebral blood flow becomes dependent on systemic blood pressure Hypoxia Hypoglycemia Falling lactate concentration Falling energy state Rise in intracranial pressure and cerebral edema
Systemic and metabolic changes	Hyperglycemia Lactic acidosis	Hypoglycemia Hyponatremia Hypokalemia / hyperkalemia Metabolic & respiratory acidosis Hepatic and renal dysfunction Consumptive coagulopathy, Multiorgan failure Rhadomyolysis, Myoglobinuria Leucocytosis
Autonomic and cardio vascular changes	Hypertension (initial) Increased cardiac output	Systemic hypoxia

	Increased central venous pressure Massive catecholamine release Tachycardia Cardiac dysrrhythmia Salivation Hyperpyrexia Vomiting Incontinence	Falling blood pressure Falling cardiac output Respiratory and cardiac impairment. (pulmonary edema, pulmonary embolism, respiratory collapse, cardiac failure, dysrrhythmia) Hyperpyrexia

.

Other laboratory abnormalities:

A number of laboratory abnormalities may be found during generalized convulsive SE.

1. A peripheral leukocytosis occur in approximately two thirds of episodes [8].
2. Acidosis is common, with an initial pH of less than 7.3 in 60-80% and a pH of less than 7.0 in 12.5 – 33% [8]. The lactic acidosis is due to glycolysis, tissue hypoxia, impaired respiration and catecholamine release [13].
3. There may be minimal elevations in CSF white blood cell count with no explanation other than SE. Woody et al found more than 5 WBCs in 5 of 20 CSF specimens obtained from children with SE who had no evidence of CNS infection. In a study by Dunn et al, 6 of 64 children had elevated CSF white blood cells ranging from 8 to 25 WBC / mm^3 [8].
4. Hormonal changes seen in SE are increased levels of Prolactin, ACTH, glucagon, growth

hormone, Insulin & Epinephrine [13].

5. Rhabdomyolysis in SE is due to persistent convulsive movements and can lead on to myoglobulinuria [13].

6. Myoglobulinuria, dehydration & shock can cause Acute renal tubular necrosis, which occasionally may end up with fulminant renal failure [13].

Stages Of Generalised Tonic Clonic Status Epilepticus:

It is convenient to divide the treatment of status into stages. This is in recognition of the fact that the risk of cerebral damage caused by seizure activity is slight in the first hour or two of status, and increases with duration of ongoing electrographic activity after this. Intially relatively simple treatment is given, but within two hours, if the epileptic activity is not under control, general anesthesia is recommended [11].

1. Premonitory Stage :

In patients with established epilepsy, there is often a prodromal period before status develops in which there is a gradual increase (over hours) in the frequency of epileptic seizures. Parenteral drug treatment during this stage will usually terminate the seizures and prevent true status developing. The conventional treatment is with either IV or Rectal Diazepam. Other alternatives include IV Lorazepam or Midazolam by Buccal or IM route [11].

2. Early Status Epilepticus :

This is the first 30 min of status. It is usual to initiate treatment with a fast acting Benzodiazepine, and Lorazepam is the drug of choice. In most episodes of status, initial treatment will be effective. Even if seizure cease, 24 hrs inpatient observation should follow. In persons without a previous history of epilepsy, chronic antiepileptic drug treatment should be introduced, and in those already on maintainence antiepileptic treatment, this should be reviewed [11].

3. Established Status Epilepticus :

There are three alternative first line treatment options, but each has drawbacks and status at this stage carries an appreciable morbidity. These are subanesthetic doses of Phenobarbitone, Phenytoin or Fosphenytoin. Athree are given by IV loading, and followed by repeated oral (Phenobarbitone or Phenytoin) or IV supplementation.

Subanesthetic doses of Benzodiazepines should not be given at this stage, as they carry the risk of respiratory depression, hypotension and sudden collapse [11].

4. Refractory Status Epilepticus :

In most patients, if seizures continue for 60 to 90 min inspite of the treatment outlined above, full anesthesia is required. The prognosis in status requiring anesthesia is much poorer, and there is a high risk of mortality and morbidity. The drugs used are Barbiturates (Thiopental), Benzodiazepines (Midazolam) and Propofol.

All the anesthetic drugs are given in doses sufficient to induce deep unconciousness; and therefore assisted respiration, intensive cardiovascular monitoring and full panoply of intensive care are essential. the depth of anesthesia should be that which abolishes all clinical and EEG epileptic

activity (often requiring sedation to the point of burst suppression on the EEG), and cerebral electrical activity by necessity be visualized, either with a formal EEG or a cerebral function monitor [11].

Management:

Three factors appear to be related to mortality and mobility of SE: 1) duration of seizures, 2) age and 3) etiology [12]. Thus the only major variable of SE that can be altered with rapid and effective treatments is its duration [15]. The longer the seizure lasts, the more difficult it will be to stop [12]. Hence it is imperative that every possible effort be taken to cease the seizures as early as possible.

Prehospital treatment:

Retrospective studies in adults and children suggest that prehospital therapy shortens the duration of SE and simplifies subsequent management in Emergency department [9].

Knudsen in 1979 found Diazepam rectal administration to be effective in the acute therapy of convulsions in children [7]. This observation has revolutionized status epilepticus management. Hoppu and Santavuori (1981) used Diazepam rectal solution in treating known seizure disorder children with prolonged seizures at home. 67% of seizures were stopped in less than 15 min [7]. However the rectal route is not always acceptable or convenient.

Although Lorazepam has also been administration rectally to treat seizures in children, studies of pharmacokinetics in adult volunteers indicated that peak concentrations attained are significantly lower and later than concentrations attained after the same dose given intravenously; dose 2 to 4 times higher than the I.V. dose, which are necessary to achieve early, effective serum concentrations, may pose the risk of prolonged toxicity [15].

Lorazepam is also used by the sublingual route for rapid effect. Yager and Seshia reported absorption of sublingual lorazepam within 20 seconds and subsequent control of serial seizures in 8 of 10 children within 15 min [15].

A clinical study in San Francisco, United States of America, compared the use of I.V. Lorazapam and I.V. Diazepam in a prehospital setting by paramedics. The authors concluded that paramedics can administer Benzodiazepines in a safe and effective manner out of hospitals in adults,

and I.V. Lorazepam was superior to Diazepam; a potential limitation is the need for refrigeration, which may limit its use outside the hospital [15]l.

Midazolam is an imadazobenzodiazepine drug, which stands out in comparison with the other benzodiazepines because it is water soluble and can be administered intramuscularly. Since its introduction as an antiepileptic agent. Midazolam has been used in the prehospital setting for SE via intravenous, intramuscular, intra nasal, rectal and buccal routes [15].

I.M. Midzolam stops seizures within 5 to 10 min. I.V. access in the prehospital setting can be difficult in certain patients who are seizing especially children, the elderly or obese patients. Intramuscular Midazolam treatment may be easier, safer, more predictable and effective treatment option than either Diazepam or Lorazepam treatment by the rectal or I.M. routes. Both Diazepam and Lorazepam by I.M. route has slower & erratic absorption and more local discomfort [15].

Scott et al were the first physicians to show that buccal / sublingual Midazolam culd be rapidly absorbed with a cerebral effect seen on EEG within 5 to 10 minutes. Buccal Midazolam appear to have some distinct advantage over rectal Diazepam [15].

O'Regan et al demonstreated decrease in epileptiform activity with intranasal Midazolam administration. However Wallace comments that children who have seizures when febrile, frequently have an upper respiratory tract infection. Nasal secretions can dilute the Midazolam solution and make it more difficult for the agent to have contact with the absorbing surface [15].

Per rectal Sodium Valproate can be given as a retention enema in a dose of 20mg/kg in children with Refractory SE [15]. This treatment option need further evaluation in the field of domicilary management of seizures.

Propofol is a rapidly acting drug with short duration of action. The first study of prehospital use of Propofol was from Helsinki in 1995 [15].

For the initial treatment of SE in the prehospital setting, Midazolam has significant potential but has limited practical experience in the community. More aggressive options, including Propofol, will have to be reserved for communities in which emergency medical services are equipped to provide cardiopneumatic support and direct physician input. Unfortunately in many communities, more basic

concerns such as delayed response time and limited funding need to be addressed before these changes can be considered [15].

Hospital Treatment:

In the hospital, therapy must address the immediate problem of

1) Stopping the seizures.

2) Providing supportive measures (supplemental oxygen) a clear airway an intravenous glucose source, etc)

3) Detecting and correcting any predisposing or precipitating factors.

4) Incorporating a drug with a long half life to prevent the recurrence of seizures once they have been arrested [12].

Supportive measures:

In all patients presenting in status, the protection of cardio respiratory function takes first priority

1) Hypoxia is much worse than appreciated and oxygen should always be administered [11].
2) Blood pressure, respiration and cardiac function are maintained to avoid hypoxic is chemic damage to the brain. Resuscitation equipments should be available [12].
3) Blood samples are obtained for electrolyte, glucose, blood urea nitrogen, calcium and magnesium measurements and if the patient has been treated previously for seizures, for antiepileptic drug level determinations [12].
4) An intravenous line is inserted for the infusion of a glucose solution to maintain the blood sugar level at approximately 150mg/dl. Fluids should be limited initially to 1,000 to 1,200ml/m^2 [12]
5) Increased intracranial pressure is treated if evident [12].

Terminating a seizure may be difficult in the presence of an uncorrected underlying derangement such as hypoxemia, hyperglycemia, electrolyte disturbances, hyperthermia, dehydration or hypotension [12]. These conditions, hence, should be detected early and corrected immediately.

Drug Therapy:

Benzodiazepines are the drugs first to be used in SE. Naquet et al and Gastaut et al were the

first to document the use of intravenous diazepam in the treatment of SE [15]. Because of its short half life due to rapid and extensive redistribution to peripheral fat stores the duration of clinical effectiveness with Diazepam is only 20 to 30 min [15]. Therefore, even if seizures are arrested, an antiepileptic drug with a longer duration of antiepileptic drug with a longer duration of action must be given [12], within 20 min [6].

Lorazepam has been compared with Diazepam in many clinical trials and is considered by many as the drug of choice for SE [15,10]. It has a different volume of distribution of the free drug; therefore its clinical effectiveness can last for several hours [15] (12-24 hours) [6]. The frequency of endotracheal intubation during SE in children who received lorazepam was significantly lower (27%) compared with those who received diazepam (73%) [16]. If seizures continue after two doses of lorazepam, additional doses are unlikely to be successful. If no response is seen within 5-7 minutes, a second drug should be added [15].

Phenytoin is the next step in treatment of SE. Fosphenytoin, is a newer addition. It is a phosphate ester prodrug of Phenytoin that is highly water soluble and buffered to a pH of 8.6 to 9.0. On reaching the vascular compartment Fosphenytoin is rapidly conveted to Phenytoin by organ and brain Phosphatases. This produces a faster administration (150mg Phenytoin Equivalents / min) and attainment of free Phenytoin level of approximately 2mg/ml in adults. There is less adverse effects (such as hypotension, phlebitis and soft tissue injury from extravasations) compared with Phenytoin [15].

In accepted protocols of SE, if the patient continues convulse after Phenytoin administration, Phenobarbitone is attempted. At doses necessary in the treatment of SE, Phenobarbitone uniformly causes some degree of respiratory depression and CNS alterations. In combination with Benzodiazepines, hypotension and respiratory depression are significant concerns. Studies have found that if there is no response to Lorazepam, a second conventional agent (Phenytoin or Phenobarbitone) will only be successful in terminating SE in an additional 3 to 7% of cases. Thus with the limited yield from a third agent and the added adverse effects of prolonging SE, there is a tendency to skip the step of Phenobarbitone [15]. Alternatively I.V. Sodium Valproate 20 to 30 mg/kg I.V. Over 5 to 10 min can be used [17]. Valproate has the added advantage of avoiding the risk of additional

adverse respiratory of hemodynomic changes in critically ill patients [18]. However, Treiman proposed directly proceeding to an agent usually reserved for the treatment of Refractory SE after failure of a first line agent, as the second and third arms of drug treatment were only successful in 9.3% of overt GCSE and 7.5% of subtle GCSE [15]. In a study comparing the four different drugs for initial therapy of SE, it ever found that Lorazepam is more likely than Phenytoin to be successful when used as the initial I.V treatment for overt GCSE. Although Lorazepam was no more efficacious than Phenobarbitone or than Dizepam and Phenytoin, it is easier to use. The risk of adverse effects like hypotension, respiratory depression or cardiac arrhythmia, appears similar with any of the four regimens if drugs are administered at a safe rate to the patient. Any of the four treatments, if successful, can protect equally well against recurrence [10]. The results of the study suggest that treatment with Lorazepam alone may be sufficient and may obviate the need for I.V. Phenytoin or Fosphenytoin loading, when SE is caused by a rapidly reversible process [9] (subtherapeutic AED concentration or metabolic derangements). However, Lorazepam followed by Phenytoin is currently the treatment preferred by many neurologist and epileptologist [9,19].

Refractory SE:

The definition of Refractory SE varies in the literature and is based on failure of appropriate medical treatment and the duration of SE. Patients are considered in Refractory SE when they have not responded to sequential treatment with a Benzodiazepine, Phenytoin and Phenobarbital (or) when the seizures continue for 60 to 90 minutes after the initiation of therapy . Aggressive intervention with anesthetic drugs is indicated and requires intensive care support and EEG monitoring [15].

Pentobarbital is a potent antiseizure drug with the most experience for short acting Barbiturates and is a standard choice for Refractory SE. The major adverse effect is severe hypotension requiring presser therapy [15].

Thiopental is the most rapidly acting Barbiturate that forms Pentobarbital as an active metabolite in the body. It is used in treatment of Refractory SE in some countries due to lack of Pentobarbital [15].

Propofol is a non Barbiturate anesthetic agent that shows efficacy in the management of

Refractory SE. Propofol is more likely to provide rapid seizure control and less likely to cause tachyphylaxis, at a lower cost when compared with Midazolam. Propofol is available as a lipid emulsion and the high lipid content should be taken into account when determining fat and caloric intake. The lipid emulsion serves as a culture medium for bacteria, raising concerns about infection, but this risk is new reduced with the addition of EDTA as a preservative [15]. However, serious doubts are being raised on the safety of Propofol in treatment of RSE. Several case reports show an increased risk of mortality following Propofol therapy. Midazolam is currently widely used for Refractory SE therapy. Trachyphylaxis occurs in some patients within 24-48 hrs and the dose may need to be increased several folds to maintain seizure control [15].

Other drugs used in RSE include Lidocaine, Clonazepam, Chlormethiazole [9], Valproic Acid in repeated boluses [18] or as continuous I.V. infusion [2] may be useful in RSE. Small children may be given mega doses of multivitamin, especially B_1, B_2, B_{12} and Biotin. Pyridoxin dependant seizures are not uncommon in infants [6].

Failure To Respond To Emergency Treatment [11]:

In the great majority of the cases, the above measures will control the seizures and the status will resolve. If drug treatment fails, there are often complicating factors.

The common reasons for treatment failure are:

1. Inadequate drug treatment :

   Insufficient dosage of drug

   Failure to initiate or continue maintainence antiepileptic drug therapy,

   resulting in recrudescence of seizures.

2. Additional medical factors :

   Medical complications can exacerbate the seizures

   Failure to treat (or identify) the underlying cause can result in intractable

   status (e.g. cerebral infection).

1. Misdiagnosis of Pseudostatus as a true epileptic status.

Complications [11]:

Complications encountered in SE often need emergency treatment in their own right. Failure to do so can perpetuate the status and worsen outcome.

The medical complications in SE are as follows :

1, Cerebral :

Hypoxic / Metabolic cerebral damage
Seizure induced cerebral damage
Cerebral edema and raised intracranial pressure
Cerebral venous thrombosis
Cerebral hemorrhage and infarction

2. Cardio-Respiratory and Autonomic :

Hypotension
Hypertension
Cardiac failure, tachy and brady dysrrhythmia, cardiac arrest, cardiogenic shock
Respiratory failure
Disturbances of respiratory rate and rhythm, apnea
Pulmonary edema, hypertension, embolism, pneumonia, aspiration
Hyperpyrexia
Sweating, hypersecretion, tracheobronchial obstruction
Peripheral ischemia

3. Metabolic and Ischemic :

Dehydration
Electrolyte disturbance (especially hyponatremia, hyperkalemia)
Acute renal failure (especially acute tubular necrosis)
Acute hepatic failure
Acute pancreatitis

4. Others :

Disseminated intravascular coagulopathy
Multi organ failure
Rhabdomyolysis
Fractures
Infection (especially pulmonary, skin, urinary)
Thrombophlebitis, dermal injury

Aim
Of
The Study

AIM OF THE STUDY

1. To study the clinical and epidemiological features of children with Generalized Convulsive Status Epilepticus.
2. To find out the complications and outcome in children with Generalized Convulsive Status Epilepticus.
3. To identify the risk factors for adverse outcome in Childhood Status Epilepticus.

Materials And Methods

MATERIALS AND METHODS

Study Centre:

The study was conducted in the Emergency Room and the Intensive Care Unit of the Institute of Child Health and Research Centre, Government Rajaji Hospital, Madurai.

Study Period:

The Study was carried out from October 2005 to September 2006, a duration of one year.

Study Design:

It is a Prospective Descriptive Study.

Case definitions:

1. Status Epilepticus is defined as a continuous convulsion lasting longer than 30min or the occurrence of serial convulsions between which there is no return of consciousness.
2. The operational definition for convulsive Status Epilepticus includes:

   a) more than 5 minutes of continuous seizures.

   b) two or more discrete seizures between which there is incomplete recovery of consciousness.
3. Generalized convulsive status Epilepticus (GCSE) can be overt or subtle.

   Overt GCSE is defined as easily visible generalized convulsion.

   Subtle GCSE is indicated by coma and ictal discharges on EEG, with or without subtle convulsive movements such as rhythmic twitching of the arms, legs, trunk, facial muscles; tonic eye deviation; or nystagmoid eye jerking.
4. Patients are considered to be in Refractory Status Epilepticus (RSE) when seizures have lasted longer than 60 min even after they had sequential treatment with a Benzodiazepine, Phenytoin and Phenobarbitone.

Inclusion Criteria:

1. Children with Generalised Convulsive Status Epilepticus (GCSE) who were brought to Emergency room or who developed Status Epilepticus during hospitalization, were included in

the study.

2. Age group selected was between 1 month and 12 years.

Exclusion Criteria:

1. All neonates were excluded from this study
2. Children with focal or non convulsive status epilepticus were not included

Methodology:

A protocol for the management of children with Generalised Convulsive Status Epilepticus was developed under the guidance of Prof.Dr.D.Meikandan, Neurologist and Professor of Pediatrics of our institute. The designed study was approved by the Ethical Committee of our hospital.

All children with Generalized Convulsive Status Epilepticus were enrolled in the study as per the criteria specified. Consent for the study was obtained from the parents or the available attenders of the child. Following a brief history and rapid evaluation, the children were resuscitated and managed as per the designed protocol. Blood samples for the biochemical estimation of glucose, urea, creatinine and bicarbonate were collected, as soon as an intravenous access was first established for management. Supportive therapy, such as inotropes and mechanical ventilation were provided, as and when required.

Detailed history and thorough physical examination were completed once the seizures were controlled. Other investigations (Lumbar puncture, EEG and CT-brain) were undertaken, as soon as the child's clinical status was stable. Additional investigations were done, as and when warranted by the child's clinical condition. Specific treatment such as antibiotics or antiviral agents was initiated, as early as possible based on the clinical suspicion and / or laboratory evaluation. All children were then followed up till their discharge from hospital or death.

The clinical response of the child to treatment, complications that developed during the course of hospitalization and the ultimate outcome of the illness were studied and documented in a printed proforma. Finally, all the data were collected, consolidated, analysed and interpreted statistically.

Results And Analysis

RESULTS AND ANALYSIS

Over a period of one year 118 children with Status Epilepticus (SE) were treated in our Institute. Of this 68 cases were boys and 50 were girls. Thus the Male to Female ratio in the study population was 1.36:1 These children ranged in their age from 31 days to 12 years. The mean age at the time of presentation was 3.73 years (±3.19 yrs) (Table1) among males and 3.04 years (±2.49 yrs) among females. Three fourth of the total cases were younger than 4 years of age and infants constituted about 35% of the total cases (Table2). All children were from Grade 3& Grade 4 Socio Economic status as per modified Kuppusamy Scale[20].

93.2% of children started convulsing elsewhere outside the hospital and were admitted in the Emergency Department with SE. Rest of the children (6.78%) developed seizures during the course of hospitalization, for some other ailment. Of the children who started convulsing prior to hospitalization, 31.82% had received some form of treatment elsewhere and then referred to our Institution for specialized care. In this prehospital treatment group, 57.14% had no details of the treatment received by them and 14.29% were given Diazepam by Intramuscular route, which is of no use in SE (Table 1).The significant observation is that in about 75% of these children, the physicians have preferred the I.M.route for drug administration.

The mean total seizure duration in the study group was 4 hours 52 minutes, which includes the one hour of mean treatment duration in the hospital (Table 3).

Generalized Tonic Clonic seizure was the most common seizure type. 25.42% of children had focal onset with secondary generalization, whereas 51.69% had generalized seizures from the begining. All other children had Myoclonic seizures (Table1). Subtle seizure activity was observed among 8% of children with GTCS.

Table :1 **SALIENT FEATURES OF THE STUDY POPULATION**

S.No.	Features	Results
1.	Total no. of cases	118
2.	Total no. of Males	68
	Total no. of Females	50
	Male : Females	1.36 : 1
3.	Age range	31 days to 12 years
4.	Mean age at presentation	
	Males	3.73 yrs (± 3.19 yrs)
	Females	3.04 yrs (± 2.49 yrs)
5.	Prehospital Treatment received	35 (31.82%)
	Inj. Fosphenytoin I.M	1
	Inj. Diazepam I.V.	2
	Inj. Phenytoin I.V.	2
	Inj. Phenobarbitone I.V	3
	Drugs as per Protocol	1
	Rectal Diazepam	1
	Inj. Diazepam I.M	5 **(14.29%)**
	I.M. Injections (Details not known)	20 **(57.14%)**
6.	Seizure onset	
	Prior Hospitalisation	110 (93.2%)
	In Hospital	8 (6.78%)

28.57%

7.	Seizure type	
	GTCS – primary	51.69%
	GTCS - secondary	25.42%
	Myoclonic	22.88%
8.	Seizure pattern	
	Continuous	55%
	Intermittent without regaining consciousness	45%
9.	Refractory Status Epilepticus	22.03%
10.	Interesting cases	
	Cerebral Palsy with Acute CNS infection	1
	Downs Syndrome with Acute CNS Infection	1
	Seizure disorder with Neem oil Encephalopathy	2
	Cerebral palsy with Neem oil Encephalopathy	1
	Arrested Hydrocephalus	1
11.	Mean duration of hospitalization	6.3 days
12.	Outcome	
	Survived	73(61.86%)
	Expired	45(38.14%)
13.	Overall mortality rate	38.14%
14.	Sequelae among Survivors	3 (4.1%)
	Right Hemiparesis	1
	HIE	2

Table :2 **AGE GROUP AND FINAL OUTCOME**

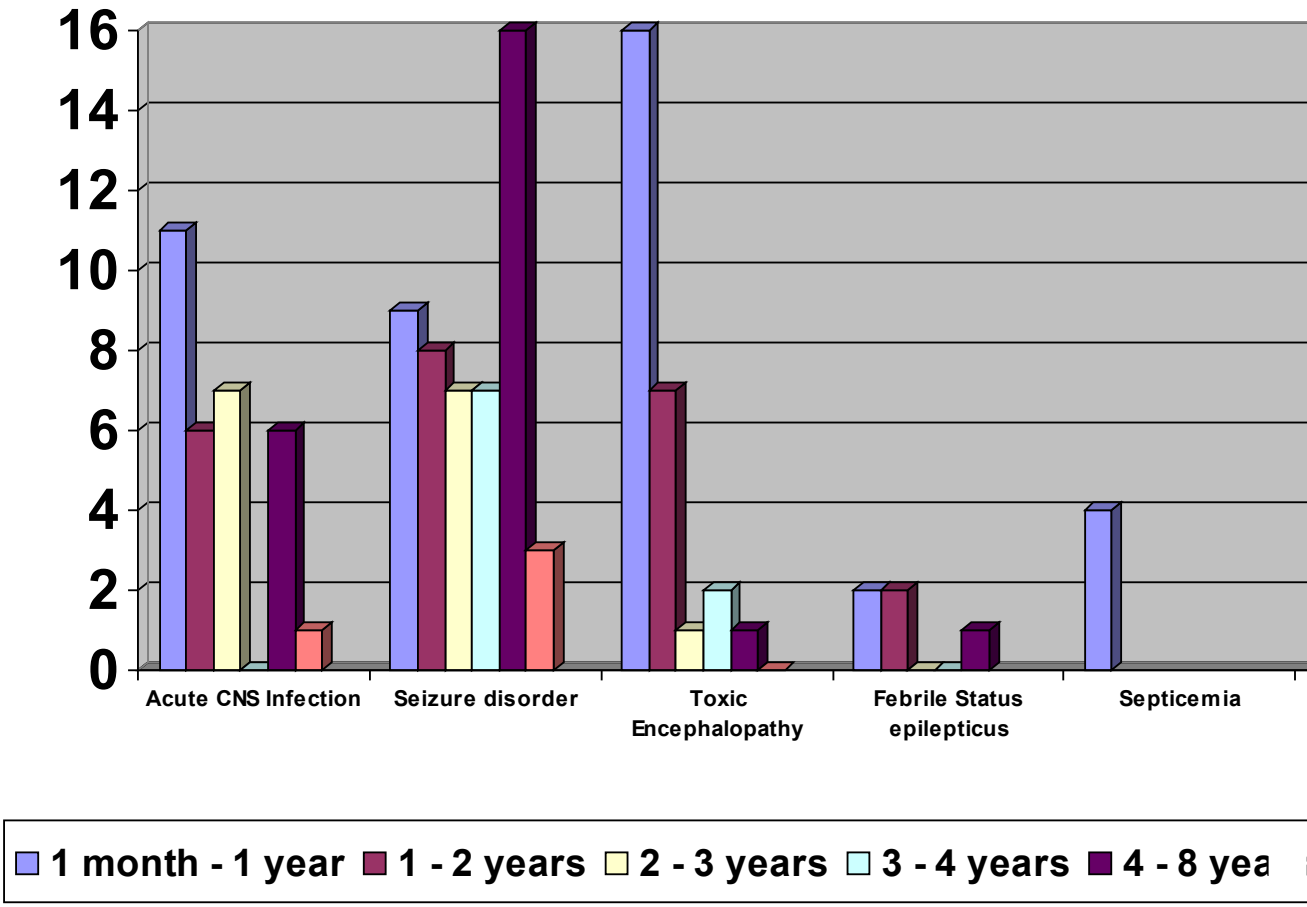
Age group	Survived	Expired	Grand total	Age specific Mortality Rate (per 100)
1mon - 1yr	21	21 **(46.67%)**	42 **(35.59%)**	50
1 – 2yrs	16	7 **(15.56%)**	23 **(19.49%)**	30.43
2 – 3 yrs	8	7 **(15.56%)**	15 **(12.71%)**	46.67
3 – 4yrs	8	1 **(2.22%)**	9 **(7.63%)**	11.11
4 – 8yrs	15	9 **(20%)**	24 **(20.34%)**	37.5
8 – 12 yrs	5	-	5 **(4.24%)**	-
Total	73	45 **(100%)**	118 **(100%)**	

Table :3 **SEIZURE DURATION AND OUTCOME**

Mean Seizure duration	Survived	Expired	Mean Total duration
Prior hospitalization	3hrs 0 min	5 hr 26min	3hr 59min
In hospital	1 hr.	1hr 23min.	1 hr 08min.
Total duration	**3 hr 56min.**	**6hr 20min**	**4hr 52min**

Chart – 1

ETIOLOGY AND AGE GROUP DISTRIBUTION



55% of the children were convulsing continuously, whereas rest of them had intermittent seizures without regaining normal level of consciousness in between (Table1).

As a whole, Seizure Disorder was the commonest cause for SE (42.37%) in the study population. This was followed by Acute CNS Infection (26.27%) and Toxic encephalopathy (22.88%). Toxic encephalopathy (n=27) includes 25 cases due to Neem oil, one case of Carbamazepine overdose and one due to herbal medicine(sangu ilai). However in infants Toxic encephalopathy was the dominant cause (38.1%) and Acute CNS Infection (26.19%) was the next common cause. Seizure disorder as a causative factor increases with advancing age of the child and more than 60% of the cases above 4 years of age were due to seizure disorder. Septicemia occurred only in infants and one

child with Hypertensive encephalopathy due to Acute glomerulo nephritis was 12 years old (Table 4)

Table 4:**AGE GROUP AND ETIOLOGICAL DISTRIBUTION**

Age group	**Acute CNS infection (31)**	**Seizure disorder (50)**	**Toxic enephalopathy (27)**	**Febrile SE (5)**	**Septicemia (4)**	**HT encephalo Pathy (1)**	**Total**
1mon -1yr	11 **(26.19%)**	9 **(21.43%)**	16 **(38.10%)**	2 **(4.76%)**	4 **(9.52%)**	-	42
1 – 2 yrs	6 (26.09%)	8 (34.78%)	7 (30.43%)	2 (8.70%)	-	-	23
2 – 3 yrs	7 **(46.67%)**	7 **(46.67%)**	1 **(6.67%)**	-	-	-	15
3 – 4 yrs	0	7 (77.78%)	2 (22.22%)	-	-	-	9
4 – 8 yrs	6 **(25%)**	16 **(66.67%)**	1 **(4.17%)**	1 **(4.17%)**	-	-	24
8 – 12 yrs	1 (20%)	3 ((60%)	-	-	-	1 (20%)	5
Total	**31(26.27%)**	**50(42.37%)**	**27(22.88%)**	**5(4.24%)**	**4(3.39%)**	**1(0.08%)**	**118(100%)**

One fourth of the cases had features of intercurrent illnessess like respiratory or gastrointestinal infections with fever, preceding the onset of SE. Such an observation was prominent in children with Acute CNS infection (61.29%) and Febrile SE (60%). All infants with septicemia were ill before they developed SE (Table 5)

Table: 5: **PRECEDING ILLNESS IN CHILDREN WITH STATUS EPILEPTICUS**

	Acute CNS infection	Seizure disorder	Toxic encepha lopathy	Septicemia	Total
Fever	7	-	-	2	**9**
Fever + URI	8	3	3	1	**15**
Fever + AGE	3	-	-	-	**3**
Fever + AGE + URI	1	1	-	-	**2**
Fever + UTI	-	-	-	1	**1**

AGE- Acute gastro enteritis; URI- Upper respiratory infection; UTI- Urinary tract infection

About 20% of children with SE responded to the first drug Lorazepam and another 31.36% to the next drug, Phenytoin. Phenobarbitone was effective in terminating the seizures in 27.12% of cases. Thus only about 22% of the seizures were not responding to the first three drugs and entered the Refractory Phase. However all refractory Status Epilepticus were controlled with progressively increasing dose of Midazolam infusion (Table 6)

Table: 6

ETIOLOGICAL DISTRIBUTION OF RESPONSE TO DRUG THERAPY AS PER PROTOCOL

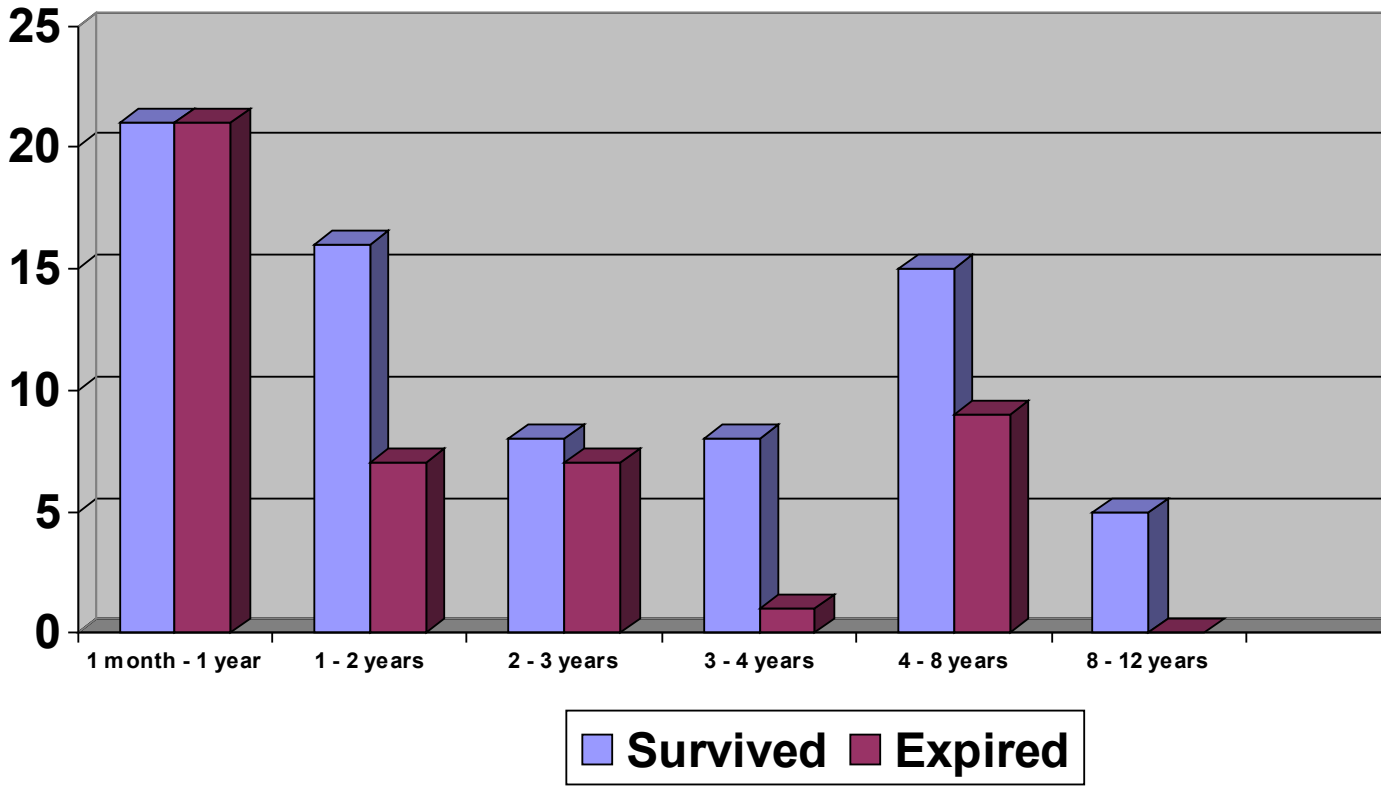
Drugs	**Acute CNS infection (31)**			**Seizure disorder (50)**			**Toxic encephalopathy (27)**			**Febrile status epilepticus (5)**			**Septicemia (4)**			**Hyperte encephal (1)**	
	S	**E**	**T**	**S**	**E**	**T**	**S**	**E**	**T**	**S**	**E**	**T**	**S**	**E**	**T**	**S**	**E**
L_1	3	-	**3 (9.68)**	7	-	**7 (14)**	2	-	**2 (7.41)**	-	-	**-**		-	**-**	-	
L_2	2	-	**2 (6.45)**	4	2	**6 (12)**	-	1	**1 (3.7)**	-		**-**		1	**1 (25)**	1	
PHT_1	1	7	**8 (25.81)**	11	-	**11 (22)**	3	-	**3 (11.11)**	2		**2 (40)**		-	**-**	-	
PHT_2	2	3	**5 (16.13)**	5	1	**6 (12)**	-	1	**1 (3.7)**	1		**1 (20)**		-	**-**	-	
PHB	3	2	**5 (16.13**	12	2	**14 (28)**	6	3	**9 (33.33)**	2		**2 (40)**		2	**2 (50)**	-	
Mid_1	3	-	**3 (9.68)**	2	3	**5 (10)**	-	5	**5 (18.52)**	-		**-**		1	**1 (25)**	-	
Mid_2	-	-	**-**	1	-	**1 (2)**	-	5	**5 (18.52)**	-		**-**		-	**-**	-	
Mid_3	-	4	**4 (12.9)**	-	-	**-**	-	-	**-**	-		**-**		-	**-**	-	
Mid_6	-	1	**1**	-	-	**-**	-	-	**-**	-		**-**		-	**-**	-	

			(3.23)														
Mid_{12}	-	-	-	-	-	-	-	1	**1 (3.7)**	1		-		-	-	-	
Total	**14**	**17**	**31**	**42**	**8**	**50**	**11**	**16**	**27**	**5**		**5**		**4**	**4**	**1**	

L- Lorazepam; PHT- Phenytoin; PHB- Phenobarbitone; Mid- Midazolam; S- Survived; E- Expired; T- Total

Chart – 2

AGE GROUP AND SURVIVAL



Of the 118 cases enrolled in the study, 73(61.86%) children survived and 45 (38.14%) succumbed to their illness. These patients remained hospitalized for a mean time period of 6.3 days. 4% of the survivors left the hospital with sequelae. The overall mortality rate among children with SE was 38.14.per 100 (Table 1). The various factors that influenced the morbidity and mortality following SE were selected and analysed statistically.

35% of the boys and 42% of the girls treated for SE expired. But this gender difference was statistically insignificant (p Value = 0.5828) (Table7).

Table 7: **Gender Distribution and Final Outcome**

Gender	Survived	Expired	Total
Male	44	24 (35.29%)	68 (100%)
Female	29	21 (42%)	50 (100%)
Total	**73**	**45**	**118**

p value = 0.5828

The mortality associated with SE was greatest (80%) in children younger than 4 years of age. This age difference was more marked in infants who accounted for 35.59% of total cases but contributed to 46.67% of total deaths. The age specific mortality rate was highest in infancy with 50 deaths per 100 infants treated (Table 2).

The mean total duration of seizure among the survivors (3 hr 56 min) was much lower than those who died (6 hrs 20 min). This is also true in the prehospital setting and following hospitalization, with survivors having shorter seizure duration. The mean seizure duration after initiating treatment was in the Refractory range (1 hrs 23 min) among the expired children (Table 3)

About 38% of children have expired both in the out-of-hospital onset group and the in-hospital onset group (Table 8).

Table 8: **PLACE OF SEIZURE ONSET AND OUTCOME**

Seizure onset	Survived	Expired	Total
Out of hospital	68 (61.82%)	42 (38.18%)	110
In hospital	5 (62.5%)	3 (37.5%)	8
Total	**73**	**45**	**118**

But in the former group about 57.14% of children who have received some treatment outside had expired. This is statistically significant (p value = 0.0097) when compared with those who visited our Emergency Department straight from their home, without being treated elsewhere (Table 9).

Table: 9

PREHOSPITAL TREATMENT AND OUTCOME IN CHILDREN WITH SEIZURE ONSET PRIOR HOSPITALISATION

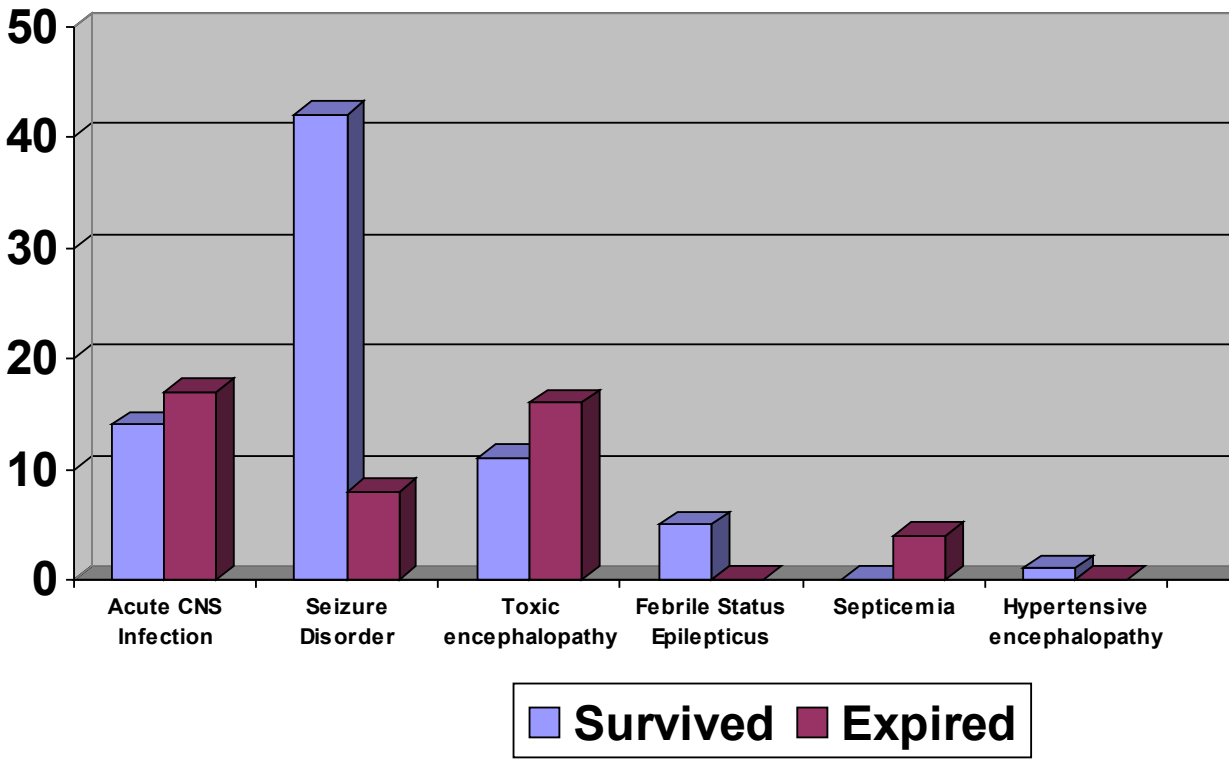
	Prehospital treatment			No Prehospital treatment			Total
	Survived	Expired	Total	Survived	Expired	Total	No.
Seizure onset prior hospitalization	15 (42.86%)	20 (57.14%)	35 **(31.82%)**	53 (70.67%)	22 (29.33%)	75 **(68.18%)**	110

p Value = 0.0097 (significant)

However, careful analysis reveals that man children who died after prehospital treatment has Acute CNS infection or Toxic Encephalopathy, the two etiologies with greater mortality rate, as discussed later. Thus the unyielding nature of the seizures due to the underlying etiology, with increased seizure duration may be the reason for this paradoxical observation.

Chart – 3

ETIOLOGICAL GROUP AND SURVIVAL



Acute CNS infection was the major contributor to mortality (37.73%) followed in close succession by Toxic Encephalopathy (35.56%). All children with Septicemia expired and none with

Febrile SE or Hypertensive encephalopathy. Toxic encephalopathy, next to Septicemia, has the highest specific mortality rate with 59.26 death per 100 and all these were due to Neem Oil ingestion (Table 10).

Table 10: **ETIOLOGICAL GROUP AND FINAL OUTCOME**

S.No.	Disease	Survived	Expired	Total No. of case	Disease specific mortality rate (per 100)
1.	**Acute CNS infection**	14	17 (37.78%)	31 **(26.27%)**	54.84
2.	**Seizure disorder**	42	8 (17.78%)	50 **(42.37%)**	16.0
3.	**Toxic encephalopathy**	11	16 (35.56%)	27 **(22.88%)**	59.26
4.	**Febrile status epilepticus**	5	-	5 **(4.24%)**	-
5.	**Septicemia**	-	4 (8.89%)	4 **(3.39%)**	100
6.	**Hypertensive encephalopathy**	1	-	1 **(0.08%)**	-
	Total	73	45	118 **(100%)**	

Children who survived of Seizure disorder and Toxic encephalopathy had a shorter seizure duration and responded earlier to the drug therapy than those who expired of the same cause. Similar observation was conspicuous by its absence in children with CNS infection (Table 11).

Table 11: **Etiological Distribution of Seizure Characteristics**

Features	Acute CNS Infection		Seizure disorder		Toxic Enceptalopathy		Febrile status epilepticus		Septicemia		Hype e en lop
	S	E	S	E	S	E	S	E	S	E	S
A) Mean Seizure duration											

1) Prehospital treatment group (no)	1	8	8	5	4	7	2				
• Out of hospital	9’30”	2’58”	5’28”	8’15”	6’55”	6’03”	2’				
• In hospital	2’	1’	50”	1’08”	50”	1’33”	45”				
• Total	11’30”	4’	6’17”	9’23”	7’45”	7’36”	2’45”				
2) Entire Study group (no)	14	17	42	8	11	16	5	-	-	4	1
• Out of hospital	5’	3’44”	4’28”	6’45”	3’59”	3’59”	1’38”			19’	4’
• In hospital	1’14”	1’	58”	1’25”	57”	1’49”	1’			1’05”	30”
• Total	6’14”	4’28”	5’25”	7’02”	4’56”	5’48”	2’38”			13’45”	4’30”
B) Post total duration	8’31”	31’58”	3’19”	17’20”	26’03”	30’11”	2’08”			30’40”	24’
C) Seizure type											
• GTCS -Primary	18 (58.06%)		32 (64%)		2 (7.41%)		4 (80%)		4 (100%)		1 (1
• GTCS-Secondary	13 (41.93%)		16 (32%)				1 (20%)				
• Myoclonic			2 (4%)		25 (92.59%)						

S – Survived ; E-Expired ; (‘) – Hours ;(“) – Minutes

The expired children had a prolonged postictal state when compared with the survivors, in all the etiological groups. Among the survivors, the children with Seizure disorder and Febrile SE were in the postictal state for a shorter period of 2 to 3 hours, whereas other cases had a postictal period lasting for many hours to days (Table 11). Drowsiness, tonic spasm of the limbs, abnormal pupillary reaction, fever and vomiting were commonly observed during the postictal period. Two seizure disorder children with focal onset of seizure developed hemiparesis on the side of seizure onset, which recovered within 24 hrs.

Myoclonic seizures were predominant in the Toxic encephalopathy group (92.59%) and this observation was statistically significant (p value = 0.0001). The generalized seizures especially the primary generalized seizures, were more in all other etiological groups (Table 11).

One fourth of the seizure disorder children responded to Lorazepam. Phenytoin was more effective to attain seizure control in Acute CNS infection (42%) and seizure disorder (34%), whereas Toxic encephalopathy required Phenobarbitone in 33% of cases and Midazolam in 40.74% of cases. Thus the incidence of Refractory SE in highest among Toxic encephalopathy group and all such cases expired. 12% of seizure disorder children and 26% of CNS infections demanded Midazolam infusion

due to Refractory status. Only 31.58% survived from Refractory SE. The maximum dose of Midazolam used in the study was 12 ug /kg/min for a child with Toxic encephalopathy, who finally succumbed (Table 6).

Complications such as shock, hypoglycemia, elevated levels of Blood urea and Serum creatnine and high Serum creatine kinase levels were noted with statistical significance in the expired children. Acidosis and hyperglycemia were more common among the survivors. All children who required inotropic and ventilatory support expired. Seizure recurrence was equal among the survivors and dead. Five children developed Aspiration Pneumonia, all in the upper region of Right lung. Thrombophlebitis occurred in four cases and five had ataxia, as a side effect of drug therapy. Three of the survivors had residual effect in the form of Hemiparesis and HIE sequelae (Table 12).

Table 12: **COMPLICATIONS IN CHILDREN WITH STATUS EPILEPTICUS**

S.No.	Complications	Live (73)	Dead (45)	p Value
1.	Shock	4 (5.48%)	8 (17.78%)	0.035
2.	Blood sugar			
	High	24 (32.88%)	6 (13.33%)	0.031
	Low	7 (9.59%)	12 (26.67%)	0.0283
3.	Urea	7 (9.59%)	22 (48.89%)	0.0001
4.	Creatinine	1 (1.37%)	13 (28.89%)	0.0002
5.	CPK	50 (68.49%)	45 (100%)	0.0001
6.	Acidosis	43 (58.9%)	14 (31.11%)	0.006
7.	Recurrent seizure	11 (15.07%)	13 (28.89%)	0.115
8.	Thrombophlebitis	-	4	0.0194
9.	Pneumonia	-	5	0.007
10.	Inotropic support	-	7	0.0008
11.	Ventilatory support	-	8	0.0003
12.	Ataxia			
	Phenytoin	4	-	0.1418
	Carbamazepine	1	-	0.6186
13.	Mean duration of hospitalization	8.36 days	2.89 days	
14.	Sequelae	3 (4.1%)		

Toxic encephalopathy had a higher incidence of shock (30%) either at presentation or during therapy. The same group had a greater need for inotropic support (18.52%) and ventilatory support (22.22%). Mechanical ventilation was also used in 6.45% of cases with Acute CNS infection. Seizure

recurrence was more in Septicemic children (50%) followed by Seizure disorder (26%) and Acute CNS infection (19.35%). Mean duration of hospital stay was longest among survivors of Acute CNS infection, mainly because of the need for prolonged antimicrobial therapy (Table 13)

45% of Acute CNS Infection were Pyogenic meningitis and rest of them were them included Aseptic meningitis and Viral encephalitis. Microbiological confirmation was passible only in 55% of pyogenic meningitis cases and 25% were due to Klebsiella species. Other organisms isolated from the CSF culture were Staphylococcus areus, Coagulase Negative Staphycococci, Escherichia coli and Citrobacter species.

In children with seizure disorder, 44% were asphyxiated at birth, 54% had delayed developmental milestones and 52% had Head circumference below the 5th percentile of Centre for Disease Control (CDC) charts[21.] Three fourth of the patients had seizures in the past and 30% had poor drug compliance. The developmental delay and poor drug compliance was more marked among the expired children. Among those children who underwent EEG and Comuputerised Tomographic (CT) scan of Brain, 97.67% and 44.19% had abnormal findings respectively (Table 14). One child, born at preterm, had fatures of arrested hydrocephalus due to old intraventricular hemorrhage (Table1). Interestingly, three children (6%) had recovered from SE in the past (Table14).

Table 13: **ETIOLOGICAL DISTRIBUTION OF COMPLICATIONS**

Complica-tions	**Acute CNS infection (31)**			**Seizure disorder (50)**			**Toxic encepha-lopathy (27)**			**Febrile status epilepticus (5)**			**Septicemia (4)**			
	S	**E**	**T**	**S**	**E**	**T**	**S**	**E**	**T**	**S**	**E**	**T**	**S**	**E**	**T**	
Shock at Presentation	1	3	**4**	2	1	**3**	1	4	**5**							
Shock during Therapy					1	**1**		3	**3**							
Inotropic support					2	**2**		5	**5**							
Ventilatory support		2	**2**					6	**6**							
Recurrent	3	3	**6**	8	5	**13**		3	**3**					2	**2**	

seizures																
Mean duration of hospitalization (days)	15.78	1.48		6.45	4.07		5.88	3.68		6.75				1.33		
Sequelae	2		**2**				1		**1**							

S- Survived; E- Expired; T- Total

Table 14: **SALIENT FEATURES OF CHILDREN WITH SEIZURE DISORDER**

S.No.	Seizure disorder	Survived (42)	Expired (8)	Total (50)
1.	H/o birth asphyxia	19 (45.24%)	3 (37.5%)	22 (44%)
2.	Delayed milestones	20 (47.62%)	7 (87.5%)	27 (54%)
3.	H.C. <5th pencentile	22 (52.38%)	4 (50%)	26 (52%)
4.	Family history positive	3 (7.14%)	-	3 (6%)
5.	Past H/o seizure	31 (73.8%)	7 (87.5%)	38 (76%)
	Poor drug compliance	10 (23.8%)	5 (62.5%)	15 (30%)
	Good seizure control	3 (7.14%)	-	3 (6%)
	Not on drugs	8 (19.04%)	-	8 (16%)
6.	Past H/o SE	3 (7.14%)	-	3 (6%)
7.	Abnormal EEG	41/42 (97.62%)	1/1 (100%)	42/43 (97.67%)
8.	Abnormal CT	19/43 (44.19%)	-	19/43 (44.19%)

H.C.- Head Circumference

About 5 ml of Neem Oil ingestion lead to seizures after an average time interval of 1 hr 42 min. In most of the cases, it was administered as a native remedy for respiratory infections. Ironically, two children received neem oil for seizure control and thus end up with SE. All children had Myoclonic seizures. The average seizure duration was 5 hr 21 min and 48% of cases progressed to Refractory

stage inspite of therapy. The neem oil encephalopathy has a very high mortality rate of 64 per 100 children (Table15).

Table 15: **SALIENT FEATURES OF CHILDREN WITH NEEM OIL ENCEPHALOPATHY**

S.No.	Variables	Survived	Expired	Meal value
1.	**Amount consumed**	5.2ml	5.46ml	**5.38ml**
2.	**Indication**			
	URI	5	5	**10 (40%)**
	AGE	-	3	**3 (12%)**
	Deworming	2	7	**9 (36%)**
	Accidental	-	1	**1 (4%)**
3.	**Time interval between consumption**	1hr 42min	1hr 42min	**1hr 42min**
4.	**% of Refractory status**	22.22%	62.5%	**48%**
5.	**Total seizure duration**	4hrs 45min	5hrs 36min	**5hr 21min**
6.	**Specific mortality rate**	-	-	**64 per 100**

The critical analysis of the study reveals the following factors to be associate with high risk for mortality in children with Status Epilepticus.

1. children less then 1 year of age carried a statistically significant risk for death (p value = 0.0343) when compared with other age group.
2. 95% of the deaths have occurred in children with total seizure duration exceeding 1 hr. When the seizures have not responded to more than 45 min of treatment in the hospital, then the risk for mortality becomes statistically significant (p value = 0.0129) (Table 16).

Table 16: **Inhospital Seizure duration and risk of mortality**

Inhospital Seizure duration	Survived	Expired
<45 min	36	11
>45min	37	34

p value = 0.0129 (significant)

3. Acute CNS infection and Toxic encephalopathy were significantly associated with higher incidence of death, compared to Seizure disorder and Febrile SE. All children with Septicemia have expired.
4. Presence of shock at the time of presentation (p value = 0.035) and the need for Inotropic support (p value = 0.0008) and ventilatory support

(p value = 0.0003) during therapy significantly raised the chances for death.

5. Development of complications such as raised blood urea level (p value = 0.0001), elevated serum creatinine level (p value = 0.0002), hypoglycemia (p value = 0.0283), pneumonia (p value = 0.007) and thrombophlepitis (p value = 0.0194) were observed more significantly in the expired group.

Discussion

DISCUSSION

The present study was compared with many other studies done in and out of India over different periods of time. This comparative analysis throwed light on various aspects of the disease such as epidemiological trend, causative factors and effectiveness of therapeutic interventions, in various parts of the world. There is not much of published data either population based or hospital based studies from the Indian subcontinent[22].

A study with similar objectives was carried out by Gulati et al at All India Institute of Medical Sciences (AIIMS), New Delhi. However it was a restrospective study and included only the children between 1 month and 10 years of age[22].

56% of patients in AIIMS study were below 5 years of age[22]. In our observation, three fourth of all our children were younger than 4 years of age. The reason for this predominance of SE in younger children is not known. Probably, mechanism for control of seizure activity are fragile in younger children and may get disrupted with minimal abnormalities in neurofunction[22]. Similarly Kroczka et al from Cracow reports that SE appeared more frequently in children diagnosed with epilepsy during the first 2 years of life[23].

Males were dominant in the Gulati et al study (male : female = 2.75:1) but the gender difference in our study was minimal (male : female = 1.36:1). Gulati et al have observed that fever, upper respiratory infection and gastroenteritis precedes many SE cases[22]. This was also noted in the present study. Oliviera et al from Portugal has identified fever as the inducing factor for SE in 27% of the cases[24].

About 60% of cases in the AIIMS study have received some treatment before reaching their emergency service and the combination of Diazepam and Phenytoin was the most commonly administered drug for the initial control of seizures[22]. In our institution, 30% of cases have received some treatment prior hospitalization and 75% of the prehospital treatment group have received IM injections and the most common therapy was IM Diazepam, in whom the treatment details were available.

The most common seizure type observed in the AIIMS study was GTCS (63.3%)[22], which is

similar to the present study (77.11%). Myoclonic seizures have contributed to 22.88% our cases, as against 6.6% of AIIMS cases[22]. This could be due to the higher incidence of Myoclonic seizures in association with Neem oil encephalopathy, an etilology unique to our region.

One third of the cases in Gulati et al study required more than three drugs to control the seizures[22], whereas 22% of our cases have not responded to the first three drugs. The incidence of Refractory SE (RSE) in the AIIMS study was higher (40%)[22], when compared with our study (22%) Prasad et al from Canada comments that longer a seizure lasts, the more difficult it becomes to control and that seizures can have immediate and long term adverse consequences on immature and developing brain[25].

All the RSE in our study were managed with Midazolam infusion and 68.42% of such children expired, yielding a morality rate of 68.42% for RSE. However meta-analysis by Gilbert et al of Refractory status eplepticus reveals that there were no deaths among children treated with Midazolam and the overall morality rate for RSE was 16%[26].

The etiology of seizures is usually analysed because this has been shown to affect the morality of SE and can affect the duration of seizures[26]. Epilepsy, followed by acute symptomatic seizures were the common causes identified in AIIMS study[22]. Whereas the reverse was true in the present study, with acute CNS infection and Toxic encephalopathy dominating the symptomatic group. Oliviera et al has made an observation similar to ours with 53% of their cases being symptomatic seizures[24].

34% of our cases (Seizure disorder – 38; Seizure disorder with Neem oil encephalopathy – 2) and 47% (14/30) of AIIMS cases[22] had seizures in the past. This sharply contradicts with the study by Sagduyu et al, Turkey[27], whose 72% of SE cases had pre existing Seizure disorder. Status Epilepticus was the first manifestation of Seizure disorder in 24% of our cases. But Lauterbach et al from Cracow, reports a higher figure with 54% of their children with epilepsy manifesting first with a status[28]. One third of our Seizure disorder cases had poor drug compliance. Sagduyu et al also reports that antiepileptic drug withdrawal is the most prominent cause for SE[27]. But Kroczka et al strongly says that discontinuation of treatment was not a reason of SE in any of their cases[23].

30 of our cases (25.42%) had developmental delay (Seizure disorder with developmental delay

– 27, cerebral palsy with acute CNS infection – 1, cerebral palsy with Neem oil encephalopathy – 1, Downs syndrome with acute CNS infection – 1). A similar incidence (26.67%) was recorded in the AIIMS study[22]. Lauterbach et al opines that the probable risk factor for SE was the association with mental retardation[28].

The overall mortality rate in AIIMS study was 30%[22] as against 38% in our study. The Neem oil encephalopathy, unique to our area may be responsible for this slightly higher mortality, because it accounted for one fifth of the total cases but to one third of death. With the exclusion of Neem oil encephalopathy(total-93; death-29), our study population mortality rate of 31% correlates well with the AIIMS study.

Margosa oil (Neem Oil) is a long chain fatty aid, extracted from the seeds of Neem[29] (Azadirachta indica)[30] and has been shown to cause a Reye-like syndrome with death from hepato encephalopathy[31]. The oil is widely used as a traditional medicine by Indians in India, Sri Lanka, Burma, Thailand, Malaysia and Indonesia and it causes toxic encephalopathy particularly in infants and young children, with recurrent generalized seizures, leucocytosis and metabolic acidosis[29]. There toxic effects might be due to presence of Aflatoxin and other toxic compounds in neem oil. The oil acts rapidly within 30 min, on the nuclei of the hepatocytes[31], uncouples mitochondrial oxidative phosphorylation, thus inhibiting the respiratory chain[30] .

Sagduyu et al reports a lower case fatality rate of 21%[27]. However the mortality rate reported in American text books is around 5%[1]. Meta analysis by Gilbert et al states that outcomes in India could be different for non drug related or etiology related reasons. For example, slow transportation to the site of medical care could both increase mortality and decrease efficacy. Differences in intensive care unit practices also could alter mortality[26]. Kroczka et al adds that the low frequency of SE in their study can be related to continuous access to pediatric neurologist and experienced nurse team[23] .

More deaths have occurred in younger children, below 3 years in AIIMS study[22] and below 4 years in our study. Males had higher mortality rate in AIIMS study[22] ,whereas there was no significant gender difference with mortality in our study.

The major determinants of fatal outcome identified by Sagduyu et al were[27]

1. increasing age
2. longer duration of SE before initiating therapy
3. CNS infection as a cause for SE

These factors correlate well with our study.

Following is the comparison of risk factors for death following SE, identified in our study and AIIMS study[22]

S.No	**Risk factors**	**AIIMS study**	**Our Study**
1	Age	<36 months	<1year*
2	Total seizure duration	>45 min*	> 1 hour
3	Response to treatment	> 1 hour	> 45 min*
4	Shock	Present*	Present*
5	Other complications		Need for inotropic support* Need for ventilatory support* Elevated blood urea & serum creatinine* Hyperglycemia* Pneumonia* Thrombophlebitis*
6	Etiology		Acute CNS infection* Toxic encephalopathy*

* - Statistically significant

Limitations Of The Study

LIMITATIONS

1. Children with head injury were not included in the study as these cases were not managed in our department.
2. Toxicological studies in children with toxic encephalopathy could not be done due to practical difficulties.
3. Antiepileptic drug level estimation could not be done due to lack of facility in our region.
4. Laboratory estimation of serum Sodium, Potassium and Magnesium were not available in our institution during the study period. Serum calcium level analysis was not available regularly on all days. As such these biochemical parameters could not be included in the study.
5. Our hospital does not have the provisions for urine myoglobin analysis.
6. Microbiological confirmation of CNS infection was not possible in majority of the cases due to technical difficulties in our set up.
7. Ventilatory therapy could not be guided by Arterial blood gas analysis due to lack of facility.
8. EEG could not be done in all cases and EEG monitoring of therapy of Refractory SE was not done due to limited resources and lack of bedside EEG monitor.
9. CT brain was not done in all children either due to the financial constraints of the parents or due to the poor general condition of the patient, preventing transport to the CT-Scan room.
10. The long term follow up could not be done due to the poor turn up of the cases for review.

Conclusion

CONCLUSIONS

1. Status Epilepticus is common pediatric neurological emergency with life threatening potential.
2. Children below 4 years of age and especially the infants were most commonly affected by Status Epilepticus.
3. Toxic encephalopathy and Acute CNS infection were the common etiology in infants, whereas seizure disorder was more prevalent in older children.
4. Toxic encephalopathy due to neem oil ingestion, as a cause for SE is unique to our Madurai region. It is common in children below 2 years and carries a high mortality rate.
5. Many children with acute CNS infection and febrile SE had a preceding febrile illness.
6. One fourth of children diagnosed as seizure disorder, had SE as the first manifestation of their disorder.
7. Among known seizure disorder children on antiepileptic therapy, one third had poor drug compliance and presented with SE.
8. Intramuscular route was the most preferred method of drug administration among the physicians, who subsequently referred the cases to our institution.
9. Longer the seizure duration, lesser the chance for early termination with drug therapy and greater the risk for death.
10. Prolonged postictal state was mainly observed among children with toxic encephalopathy and acute CNS infection.
11. Presence of shock, respiratory depression, aspiration pneumonia and renal failure significantly increases the risk for death.
12. Toxic encephalopathy and Acute CNS infections have a higher mortality rate and were the major contributors in expired group.

Recommendations

RECOMMENDATIONS

1. Parents of Seizure Disorder children are to be educated about the need for strict drug compliance and the significance of early hospital visit, if the seizures go uncontrolled for more than few minutes.

2. In children with poor seizure control inspite of good drug compliance, training the parents to administer Rectal Diazepam at home, in the prescribed dose can be considered.

3. There is an urgent need for public awareness campaign in this region, about the harmful effects of Neem oil administration to the children.

4. The Intramuscular Midazolam may be preferred for the emergency management of Status Epilepticus by the physicians in office set up, as there is a difficulty in establishing an intravenous access in a convulsing child and rectal administration of Diazepam may not be socially acceptable.

5. The supportive facilities for the management of Status Epilepticus such as Vital signs monitors, appropriate biochemical investigations and electrophysiological studies (Bedside EEG) needs further improvement.

6. The early recognition and intensive management of shock and respiratory depression may improve the survival of children with Refractory Status Epilepticus.

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Protocol

MANAGEMENT PROTOCOL FOR GENERALISED CONVULSIVE STATUS EPILEPTICUS

Airway:

Open Airway (Head tilt & Chin lift)

Jaw thrust & Cervical spine stabilization, if trauma is suspected.

Oropharyngeal suction, NG tube decompression, insert airway adjunct.

Breathing:

Spontaneous breathing: O_2 through mask – 10Lit / min.

Apneic: Bag & Mask ventilation with O_2 – 10 Lit / min.

Circulation:

I.V. Access (if possible 2 I.V lines)

Collect blood samples for glucose, urea, creatinine, electrolyte & calcium

Correct shock, if present, with NS 20ml / Kg bolus

Administer I.V. bolus of Dextrose (2ml / kg of 25% D (or) 5ml/kg 10% D)

Record body temperature & BP

(Please note the time of starting each Antiepileptic drug & time when obvious seizures ceases)

0 min: Inj.Lorazepam (I dose) 0.1mg/kg I.V., @ 2mg/min, Max.4mg/dose

↓

10 min: Inj.Lorazepam (II dose), same dosage

↓

20 min: Inj. Phenytoin (I dose) – 20mg/kg I.V. Max. dose 100mg, @ 1mg/kg/min, Max. rate 50mg/min

Total dose to be diluted in 10ml of NS & infused @ 0.5ml/min

Monitor HR, BP & Perfusion

↓

40 min: Inj.Phenytoin (II dose) 10mg/kg I.V., @ 1mg/kg/min

↓

60 min: Inj. Phenobarbitone (I dose) 20mg/kg I.V., @ 2mg/kg/min

Total dose to be diluted in 10ml & infused @ 1ml / min

Intubate the child electively & Provide Assisted ventilation

REFRACTORY STATUS EPILEPTICUS

Inj.Midazolam

0.2mg / kg I.V. bolus followed by continuous I.V. infusion @ 1 µg / kg / min, increasing by 1 µg / kg / min every 15 min till a maximum of 18 µg / kg min or seizure control. The optimum rate of seizure control is maintained for a period of 12 hrs. Subsequently the infusion rate is gradually decreased by 1 µg / kg / min every 2 hrs and then weaned off.

(Midazolam infusion preparation

6mg in 100ml of 5% D

Body wt in kg = No. of microdrops / min

→ deliver 1 µg / kg / min)

Closely monitor Haemodynamic status – HR, BP, CRT & Urine output.

Inotropic support may be needed.

Inj. Dopamine infusion - Start with 10 µg / kg / min & can be increased upto 20 µg/kg/min

(Dopamine Infusion Preparation:

6 x body wt. (kg) = mg of Dopamine added to NS to make total volume of 100ml

1ml / hr → deliver 1 µg / kg / min)

Seizure not controlled with maximum dose of Midazolam

↓

BARBITURATE COMA

↓

Inj. Thiopentone

4mg / kg loading dose over 2 min followed by

continuous I.V. infusion @ 0.2mg / kg / min,

increasing by 0.1 mg / kg / min every 5 minutes

till the seizures are controlled or a maximum dose

of 10mg / kg / min. Barbiturate coma is maintained

for 12 hrs of Seizure control & then weaned off.

(Thiopentone Infusion Preparation

300 mg in 50ml of 5% D

Body wt. in Kg = No. of microdrops / min

→ deliver 0.1mg / kg / min)

General Anaesthesia with Halothane or Isoflurane.

Proforma

STATUS EPILEPTICUS - CLINICAL PROFILE AND MANAGEMENT PROFORMA

Name : Address:

Age :

Sex :

Hospital No. :

Date of Admission :

Date of Discharge/ Death : Informant:

Unit : Reliability:

Time of Admission :

Reason for Admission : Convulson / Postictal / Others

HISTORY OF PRESENT ILLNESS :

Seizures : Time & Date of Onset :

Type : generalized / focal / focal with secondary generalization

Pattern : Tonic / Clonic / Tonic-clonic / myoclonic / subtle

Periodicity : Continuous / Intermittent

Associated features : sphincter incontinence

frothing from mouth

vomiting

injuries

cyanosis

TRIGGERING FACTORS :

Fever - duration :

Nature :

AED compliance :

Others :

Treatment given outside, if any :

ASSOCIATED SYMPTOMS :

Head ache

Visual disturbances

Vomiting

Head injury

Respiratory infection : URI / LRI / Pneumonia

GIT infection : diarrhea / dysentery

Renal : dysuria / oliguria / hematuria

Skin lesions :

Drugs / Toxins :

PAST HISTORY :

H/O seizures :

Age of onset :

Clinical type :

Evaluation details : EEG

Imaging study

Neurologists Opinion :

Current treatment :

Drug Compliance : good / poor

Seizure control : good / poor

Last episode of seizure :

Status epilepticus,if any :

H/O exanthematous illness

H/O drug intake(other than AEDs)

H/O drug reactions or allergies, if any

H/O pica

H/O contact with TB

H/O hospitalisation

ANTENATAL HISTORY :

BIRTH HISTORY:

Mode of Delivery

Birth asphyxia

Birth weight

Term / Preterm

NEONATAL HISTORY:

Seizures

Jaundice

Letharginess / feeding difficulty / vomiting

Hospitalisation, if any :

DEVELOPMENTAL MILESTONES:

Normal / Delayed / Regression

IMMUNISATION HISTORY:

Appropriate for age / missed :

Date of last Vaccination :

Additional vaccines, if any : HIB / HB / Chicken Box / ARV

FAMILY HISTORY:

Consanguinous / Non Consanguinous parents

Health & Development of siblings

Seizures

Neurological disorder

Pedigree Chart

SOCIO ECONOMIC STATUS:

Modified Kuppusamy's scale

EXAMINATION:

Level of Consciousness : comatose / stuporous / drowsy / convulsing

Description of convulsion:

Generalised : tonic-clonic / tonic / clonic / myoclonic

Subtle : Muscle twitching - Face
Limbs
Trunk

Tonic eye deviation

Nystagmus

Respiration : rapid / shallow / apnea

: regular / irregular

: Cyanosis

Peripheries : warm / cold

Peripheral pulses : bounding / normal / feeble

Injuries :

Hydration : fair / dehydrated

Dysmorphology :

Vital Signs: **Anthropometry**

RR - Weight -

PR - Length -

Temp - HC-

BP - CC-

CRT - AF -

TREATMENT

Time **Seizure** **Drugs**

Total duration of seizures :

POSTICTAL STATE :

Duration of drowsiness :

Neurological deficit :

Vomiting :

Automatic behaviour :

Fever :

Head ache :

Myalgia :

Urine output : adequate / reduced

Urine Colour : clear / yellow / red

CENTRAL NERVOUS SYSTEM :

1. Higher Functions : Conscious / drowsy / stuporous / comatose

2. Cranial Nerves :

II : Pupils

: Fundi

III, IV & VI : EOM

VII :

Others :

3.Motor System : **Right** **Left**

Bulk - UL

- LL

Tone - UL

- LL

Power - UL

- LL

Involutary Movements :

4.Sensory System :

5.Reflexes :

a) Superficial

Corneal

Conjunctival

Abdominal - upper
lower

Cremasteric

Plantar

b) DTR

Upper Limb

Lower Limb

c) Primitive Reflexes :

6. Cerebellar Signs :

7. Spine and Cranium

8. AF - Normal / Tense

9. Meningeal Signs

RESPIRATORY SYSTEM :

B/L air entry

Breath sounds

Added sounds

CARDIO VASCULAR SYSTEM :

Apical impulse

Heart sounds

Added sounds

Murmur

ABDOMEN :

Liver

Spleen

Any other mass :

Bowel sounds

CLINICAL DIAGNOSIS :

INVESTIGATIONS

1. Blood - Sugar
   - Urea
   - Creatinine
   - Bicarbonate
2. Sr.CPK
3. EEG
4. Imaging Studies (CT brain)

5. Others

Additional Treatment:

Maintenance AED therapy:

Other Drugs:

COMPLICATIONS:

1. Recurrent seizure
2. Drug adverse effect
3. Others

OUTCOME :

Discharge : Neurological status

Maintainence AED

Death : Cause of death.

FINAL DIAGNOSIS:

COMMENTS:

Master Chart

MASTER CHART

AGE AND GENDER WISE DISTRIBUTION OF CASES IN EACH ETIOLOGICAL GROUP

Etiology & Age group	Survived			Expired			Grand Total
	Male	Female	Total	Male	Female	Total	
1. Acute CNS infection							
1 mon – 1yr	2	3	**5**	1	5	**6**	11
1 – 2 yrs	3	-	**3**	3	-	**3**	6
2 – 3 yrs	2	2	**4**	-	3	**3**	7
3 – 4 yrs	-	-	**-**	-	-	**-**	0
4 – 8 yrs	1	-	**1**	1	4	**5**	6
8 – 12 yrs	-	1	**1**	-	-	**-**	1
Total	**8**	**6**	**14**	**5**	**12**	**17**	**31**
2. Seizure disorder							
1 mon – 1 yr	3	5	**8**	-	1	**1**	9
1 – 2 yrs	5	3	**8**	-	-	**0**	8
2 – 3 yrs	-	4	**4**	1	2	**3**	7
3 - 4 yrs	4	3	**7**	-	-	**-**	7
4 – 8 yrs	8	4	**12**	3	1	**4**	16
8 – 12 yrs	3	-	**3**	-	-	**-**	3
Total	**23**	**19**	**42**	**4**	**4**	**8**	**50**
3. Toxic encephalopathy							
1 mon – 1 yr	5	1	**6**	7	3	**10**	16
1 – 2 yrs	2	1	**3**	4	-	**4**	7
2 – 3 yrs	-	-	**-**	-	1	**1**	1
3 - 4 yrs	-	1	**1**	1	-	**1**	2
4 – 8 yrs	1	-	**1**	-	-	**-**	1
8 – 12 yrs	-	-	**-**	-	-	**-**	-
Total	**8**	**3**	**11**	**12**	**4**	**16**	**27**
4. Febrile status epilepticus							
1 mon – 1 yr	2	-	**2**				2
1 – 2 yrs	1	1	**2**				2
2 -3 yrs	-	-	**-**				-
3 – 4 yrs	-	-	**-**				-
4 – 8 yrs	1	-	**1**				1
Total	**4**	**1**	**5**				**5**
5. Septicemia							
1 mon – 1 yr				3	1	**4**	4
6. Hypertensive encephalopathy							
(12 yr)	1	-	**1**				1

List Of Abbreviations Used

LIST OF ABBREVIATIONS

1.	CNS	-	Central Nervous System
2.	ECG	-	Electrocardiogram
3.	EEG	-	Electroencephalogram
4.	GCSE	-	Generalized Convulsive Status Epilepticus
5.	GTCS	-	Generalized Tonic Clonic Seizures
6.	HIE	-	Hypoxic Ischemic Encephalopathy
7.	hr	-	Hour
8.	ILAE	-	International League Against Epilepsy
9.	I.M	-	Intra Muscular
10.	I.O	-	Intra Osseous
11.	I.V	-	Intra Venous
12.	kg	-	Kilogram
13.	mg	-	Milligram
14.	min	-	Minute
15.	ml	-	Milliliters
16.	NCSE	-	Non Convulsive Status Epilepticus
17.	NMDA	-	N-Methyl d-Aspartate
18.	RSE	-	Refractory Status Epilepticus
19.	SE	-	Status Epilepticus
20.	yrs	-	Years